replacing at least one amino acid of enzyme with the proviso that the activity of the chimeric enzyme is modulated upon binding of a binding molecule to the binding site moiety, (2) test sample containing said analyte of interest, and (3) a substrate upon which the chimeric enzyme catalytically acts; and

detecting the amount of catalysis of the substrate and thereby determining the presence or absence of said analyte of interest.

35. A method of claim 34, wherein the analyte is an antibody.

37. (Amended) The method of claim 30, wherein the enzymatic activity of the chimeric enzyme in the unbound state is equivalent to that of the β-lactamase.

38. (Amended) The method of claim 34, wherein the enzymatic activity of the chimeric enzyme in the unbound state is equivalent to that of the β-lactamase.

Please cancel claim 36 without prejudice.

REMARKS

Claims 13-38 were pending. With this Amendment, claim 36 has been cancelled without prejudice and claims 30-35 and 37-38 have been amended by limiting the starting enzyme in those claims to β-lactamase as suggested by the Examiner. A marked up version of specifically amended claims 30, 34, 37 and 38 is provided as Exhibit A. Thus, claims 13-35 and 37-38 are currently pending.

The following issues remain from the Office Action:

a) Claims 13-38 were rejected under the "enablement" requirement of 35 USC 112, first paragraph;

b) Claims 13-38 were rejected under the "written description" requirement of 35 USC 112, first paragraph;

c) Claims 13, 20, 30 and 34 were rejected under 35 USC 102(a) for anticipation by Benito et al., JBC 271(5): 21251-21256 (1996); and

d) Claims 13, 20, 30 and 34 were rejected under 35 USC 102(b) for anticipation by Brennan et al., Protein Engineering 7(4): 509-514 (1994).

For reasons explained below, Applicants respectfully traverse each of these aforementioned rejections.

A. Claims 13-38 Are Fully Enabled

Claims 30-38 were amended pursuant to the Examiner's suggestion. As such, the amendment is believed to alleviate all reasons for rejection of claims 30-38 and withdrawal of this rejection is respectfully requested.

The Examiner states that that "the guidance provided for a single site specific chimeric β-lactamase is inadequate for one skilled in the art to develop a method using any chimeric enzyme construct for determining the presence or amount of an analyte in a test sample" (Office Action, page 2).

Applicants respectfully traverse. There is no requirement that an applicant provide a working example of his invention. See *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982). In addition to the disclosure in working Examples 1-3, the subject specification provides an extensive disclosure of suitable target molecules on pages 2-3 and a description of the methods necessary to modify the starting target molecules on pages 8-9 (See, Specification at pages 2-3, 8-10). In the preferred embodiment of the instant invention, the R-TEM β-lactamase chimera was actually reduced to practice as indicated by working Examples 1-

3 (See, Specification at Examples 1-3, pages 20-29) and production of the other compounds of the currently pending claims is within the purview of a skilled artisan.

The selected references submitted previously for the Examiner's convenience describe engineering of five distinct enzymes such as alkaline phosphates, β-glycosidase, thioredoxin, staphylococcal nuclease and β-lactamase having epitopic sequences inserted in the original sequence of the enzyme to modulate the enzyme activity. The distinct advantages of the mimetope selection and insertion in place of the epitope are described in the specification on pages 10-11. For example,

> An advantage of employing a mimetope is that no knowledge of the structure of the epitope is required. This knowledge is in general difficult to acquire, particularly if the epitope is non-linear.

[Specification, page 11]

However advantageous the use of the mimetope is, the technical challenges are no greater than those for using epitopic sequences. Therefore, Applicants submit that one of ordinary skill in the art would be able to practice the presently claimed subject matter in view of the specification and the prior art without undue experimentation. Working examples are not required to satisfy the enablement requirement (MPEP Section 2164.02).

The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976). See also, MPEP § 2164.01. The fact that experimentation may be complex does not necessarily make it undue if those skilled in the art typically engage in such experimentation. *In re Certain Limited - Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983); *M.I.T. v. A.B. Fortia*, 227 U.S.P.Q. 428 (Fed. Cir. 1985); *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). See also, MPEP § 2164.01.

Thus, the specification need not provide examples or specific description of embodiments for the entire scope of the invention. Detailed procedures for making and using an invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention [MPEP §2164]. A patent does not teach, and preferably omits, what is well known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). [See also, MPEP § 2164.01].

While acknowledging the construct described in working Examples 1-3, the Examiner states that "the transfer of such a construct to any enzyme from any source in order to first produce a chimeric enzyme and further attempt to selectively insert mimetopes pertinent to any enzyme in order to create a chimeric enzyme which can successfully attach itself to binding molecules, lacks adequate guidance, is unpredictable and would result in undue experimentation" (Office Action, page 3).

Applicants respectfully submit that it is unclear what the basis of this assertion is.

First, it is unclear what is meant by "transfer of such a construct to any enzyme from any source in order to first produce a chimeric enzyme and further attempt to selectively insert mimetopes pertinent to any enzyme in order to create a chimeric enzyme." Insertion of a mimetope into the native enzyme sequence creates a chimeric enzyme according to the present invention. There is no "transfer of such a construct ... in order to first produce a chimeric enzyme." The insertion is what produces a chimera. The present specification provides clear guidance to allow a person of ordinary skill in the art to select a starting enzyme and a mimetope, select an insertion site and thereby produce chimeras.

As discussed by the Examiner (Office Action, p. 3), with respect to Wand factors (a) (the quantity of the experimentation necessary) and (b) (the amount of direction and guidance presented), contrary to the Examiner's assertions, the quantity of experimentation necessary to practice the claimed invention would not be great or undue.

Applicants notes that the Nobel Prize for gene splicing was awarded to Paul Berg in 1980, well before the filing of the present application. Therefore, the production of chimeric enzymes was well within the purview of one of ordinary skill in the art and the technique was well developed at the time the present application was filed. Furthermore, Applicants have specifically pointed out the methods and referenced the methods relevant to practicing the instant invention in the detailed description of the specification (See, Specification, pages 2-6 and Examples 1 and 3).

More specifically, the specification clearly teaches a skilled artisan to select a starting enzyme and a binding site moiety insertion site (e.g., a mimetope insertion site) at a location preferably remote from the active site of the enzyme. The use of a site selection remote from the active site preserves the activity of the starting enzyme in the chimeric construct. The information relating to the activity of enzymes of interest and methods of measuring enzyme activity is known to one of ordinary skill in the art and available through multiple public and commercial databases. In addition, the specification provides 78 examples of mimetope sequences. Selecting a specific mimetope is also within the purview of one of ordinary skill in the art. The specification also provides sufficient disclosure and guidance to enable a person of ordinary skill in the art to obtain such a chimeric enzyme without undue experimentation (Specification, pages 2-9).

Furthermore, Applicants urge that specific sequence or structure information, as well as a specific insertion site selection is unnecessary for modifying a starting enzyme for the desired activity. A chimera that retains the activity of the starting enzyme can be identified with routine screening and without undue experimentation.

The MPEP clearly states:

> As long as the specification discloses **at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim**, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed.Cir.), *cert. denied*, 484 U.S. 954 (1987).

[MPEP 2164.01(b), emphasis added]

Therefore, Applicants maintain that the amount of experimentation necessary to practice the instant invention is not undue, because of the amount of guidance provided in the specification, the level of skill in the art, and the fact that individuals of ordinary skill in the art regularly engage in such experimentation as evidenced by cited references.

Therefore, one of ordinary skill in the art would be able to practice the presently claimed subject matter in view of the specification and the prior art without undue experimentation.

With respect to factor (c) (the presence or absence of working example), Applicants submit that the specification need not provide working examples or specific description of embodiments for the entire scope of the invention. Detailed procedures for making and using an invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention [MPEP §2164]. A patent does not teach, and preferably omits, what is well known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir.

1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). [See also, MPEP § 2164.01].

The subject specification provides working examples 1-3 and the enabling description of methods of making and using an invention. Therefore, it is improper to reject claims on the ground that the specification does not support the claims when the terms of the claim are no broader than the broadest description of the invention in the specification and there is no reason to challenge the operativeness of the subject matter embraced by the claims. *Ex parte Altermatt*, 183 U.S.P.Q. 436 (POBA 1974). Moreover, there is no requirement that an applicant provide a working example of his invention. See *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982). Thus, the fact that the working examples are limited to the use of β-lactamase does not provide a sufficient basis to reject the present claims. The working examples, in combination with the entire disclosure and the level of skill in the art, demonstrate the enablement of the claimed subject matter.

With respect to factor (d) ("the nature of the invention") and factor (e) ("the state of the prior art"), Applicants respectfully submit that the instant invention is a development in the field of preparing chimeric proteins. As such it is building on the art of chimeric enzyme production which used epitopes and was well developed at the time the present application was filed and not unpredictable. Review article published subsequent to the filing date of the application shows a number of references to enzymes engineered to have a regulatable activity both prior and past the filing date of the subject application (Legendere D et al., (1999), *Nature Biotechnol*, 17: 67-72 and Skerra A, (2000), J Mol Recognition, 13: 167-187).

With respect to factor (f) ("the relative skill of those in the art") and factor (g) ("the predictability and unpredictability of the art"), Applicants submit that while "every enzyme is

distinct" in the field of the invention, this fact does not necessarily make the field unpredictable. The success of the field of enzyme catalysis and enzyme engineering prior and subsequent to the instant application is indicative of the predictability of the art. Applicants respectfully submit that the disclosure of the current invention in view of the high state of the skill of those in the art of chimeric enzyme catalysis, evidenced from the submitted references, establishes that the present invention is indeed operable, controllable and reproducible, and well within the purview of one of ordinary skill in the art.

Finally, with respect to factor (h) (breadth of the claim), Applicants respectfully traverse. As stated above, the "enablement" prong of the first paragraph of 35 U.S.C. §112 requires nothing more than objective enablement. Whether this is achieved by illustrative examples or by broad terminology is of no importance. *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971).

Even assuming *arguendo* that a reasonable basis for objecting to the specification was set forth in the Office Action, the description provided in the specification is sufficient to overcome the objection. The specification describes how the amino acid sequence of an enzyme can be modified by insertion of a mimetope at a location which is preferably remote from the active site of the enzyme. Alternatively, the enzyme can also be modified by replacing one or more amino acids with the mimetope sequence. These modifications will yield a chimeric enzyme with activity equivalent to the original starting enzyme and the activity level is modulated upon the binding of a binding molecule to the mimetope. The specification on pages 2-9 provides disclosure and guidance in obtaining such a chimeric enzyme. The method has been demonstrated using a particular species of β-lactamase enzymes although it is generally applicable to a broad range of starting molecules such as β-lactamase, plasmin, prostate specific antigen, subtilisin, alkaline phosphatase, β-galactosidase, glutathione transferase, staphylococcal

nuclease, lysozyme, a catalytic antibody, esterases, pyruvate kinase, glucose oxidase, lactate dehydrogenase, glucose 6-phosphate dehydrogenase or luciferase as described in the specification on p. 5-6.

With the availability of a library of mimetopes and the routine screening methods available to those skilled in the art, specific information about sequence homology or functional similarity among different enzymes to modify a starting enzyme for the desired activity is not required.

Enablement is not precluded by the necessity for experimentation such as routine screening. *In re Wands*, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). The following case law and MPEP citations further explains the extent to which experimentation is permitted.

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988) and MPEP 2164.06.
>
> The test for enablement is whether one reasonably skilled in the art to make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. A patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988).
>
> The enablement requirement is met if the patent application enables "any mode" of making and using the claimed invention. *William Service Group, Inc. v. O.B. Cannon & Son, Inc.*, 33 U.S.P.Q. 2d 1705, 1723 (Eastern District of Pennsylvania 1994). A patent application may be enabling even though some experimentation is required, but the amounts of experimentation must be reasonable. Id.
>
> An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. *In re Colianni*, 561 F.2d 220, 224, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977), MPEP 2164.06.

Therefore, it is respectfully submitted that one of ordinary skill in the art would only require routine experimentation to practice the disclosed invention.

In rebutting the Applicants arguments, the Examiner relies on the MINIREVIEW by Bush et al. in *Antimicrobial Agents & Chemotherapy* 39(6): 1211-1233 (1995) as supporting the conclusion "a modification made in one type of the β-lactamase having a specific sequence may not necessarily translate to or appropriate to make in another kind of β-lactamase or any other enzyme" (Office Action, p.7).

In the Bush et al. article (p. 1217, col. 2, 2nd para. lines 5-7) the authors state that "...β-lactamases are known to encompass a great deal of diversity in the number of amino acid substitutions that **can be tolerated** with the retention of β-lactam-hydrolyzing activity...". It is the structural similarities of the β-lactamases that retains the enzyme's functional activity despite differing sequences that are an important factor to consider. A person of ordinary skill in the art will readily determine the modifications of the mimetope and the position of an insertion site from a sequence of a starting enzyme and structural information available. Such analysis is routine in the art of chimeric enzymes and there are multiple computer algorithms available to assist a skilled artisan. The invention is not limited to β-lactamases but is generally applicable to any enzyme. Guidance and direction is provided in the specification to determine the structure of the enzyme and the disclosure provides the appropriate screening methods for generating a library of mimetopes. Therefore, focusing only on the differing enzyme sequences is largely irrelevant to the operability of the invention and its enablement.

The Examiner further argues that while the specification teaches how "employing the 3-dimensional structure is one of the techniques that is used for selecting and specifically identifying a desired location on the molecule to be engineered (Specification, page 14)", "X-ray

crystallography is still very much a complicated and an unpredictable art and therefore the reliance upon such a technique for elucidating the 3-D structure of any protein and extending the teachings of a chimeric β-lactamase to any enzyme without adequate guidance is unreasonable, undue and not enabled" (Office Action, page 8).

Applicants respectfully disagrees. The specification does not teach or suggest that determining a 3-D structure is routine. The 3-D structures of hundreds of proteins were readily available to a skilled artisan at the time the present application through public databases such as Protein Data Bank (http://www.rcsb.org/pdb/). Therefore, the skilled artisan would have had an access to the sequence and structure information for this protein without engaging into crystallographic research. Even assuming *arguendo* (without admission) that crystallographic information is not available for a number of enzymes, a number of non-working embodiments are allowable (See, MPEP 2164.08(b)).

In any case, the specification provides clear enabling description for a number of methods which do not require structural information. The alternative approach to three-dimensional structure analysis is to select target molecular sites that are susceptible to limited proteolysis or sites strongly predicted to be loops by secondary structure prediction or by analysis of hydrophobic patterns suitable for insertion or replacement engineering (Specification, pages 14). Another alternative approach is to engineer a binding site moiety at random positions within the target molecule followed by routine screening for enzymatic activity.

One of ordinary skill in the art would readily recognize that screening, structural analysis and limited proteolysis analysis are not specific to β-lactamase and can be used with any starting enzyme without undue experimentation.

Accordingly, Applicants submit that the presently claimed subject matter is fully enabling to one of ordinary skill in the art. Therefore, withdrawal of the rejection of the claims under 35 USC 112, first paragraph, is respectfully requested.

B. Claims 13-38 Satisfy The Written Description Requirement

Claims 30-38 were amended pursuant to the Examiner's suggestion. As such, the amendment is believed to alleviate all reason for rejection of claims 30-38 and withdrawal of this rejection is respectfully requested.

The Examiner states that "the specification does not describe a representative number of species to the genus. A 'representative number of species' requires that the species which are expressly described be representative of the entire genus" (Office Action, page 9).

Applicants respectfully traverse. While the specification provides a working demonstration using a particular species of β-lactamase enzymes, it also describes a broad range of species such as β-lactamase, plasmin, prostate specific antigen, subtilisin, alkaline phosphatase, β-galactosidase, glutathione transferase, staphylococal nuclease, lysozyme, a catalytic antibody, esterases, pyruvate kinase, glucose oxidase, lactate dehydrogenase, glucose 6-phosphate dehydrogenase or luciferase (See, Specification, pages 5-6). The Examiner appears to disregard the written description for species other then those reduced to practice. Contrary to the Examiner's assertion, the MPEP clearly states:

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or

> structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct.304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

[MPEP 2163, emphasis added]

Applicants respectfully submit that the claims of instant invention are not limited to β-lactamases, which is provided exclusively as an example. "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." (*Reagents of the University of California v. Eli Lily*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); See also, MPEP 2163.

The specification clearly defines what Applicants regard as their invention: "In accordance with the present invention, a desired target molecule (TM) can be modified to have at least one binding site moiety (BSM) to which a binding molecule (BM) can attach" (Specification, page 2, lines 10-12). The specification describes the present invention in terms of a generic target molecule (which elsewhere in the specification Applicants note could be an enzyme). The target molecule is modified to have a binding site moiety (which elsewhere in the specification is described as preferably being a mimetope). Nowhere in the specification do Applicants limit the target molecule of their invention to an enzyme and in particular to β-lactamase. On the contrary, the specification names more than ten examples of what can be used as a target molecule (Specification, page 2 line 23 – page 3, line 11).

Applicants urge that the function of the written description requirement is to ensure that a patent is granted to inventors who had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by them; how the specification accomplishes this is not material. *In re Smith*, 178 U.S.P.Q. 620 (CCPA 1973), emphasis added. (See also, *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117). Therefore, the test for written description under 35 U.S.C. §112, first paragraph, is whether the originally filed specification reasonably conveys to a person having ordinary skill that Applicants had possession of the subject matter later claimed. *In re Kaslow*, 217 U.S.P.Q. 1089 (Fed. Cir. 1983). [See also, MPEP, Section 2163.02].

Applicants urge that a person of ordinary skill in the art would recognize from the disclosure in the specification that Applicants were in possession of the instant invention at the time the application was filed. Namely, Applicants were in possession of a method for producing chimeric enzymes having regulatable activity by inserting a mimetope sequence in the starting sequence of the enzyme and were in possession of a method of using chimeric enzymes to measure presence or the amount of an analyte.

Therefore, Applicants respectfully request that this rejection be withdrawn.

C. Applicants Claims Are Novel Over Benito and Brennan

Applicants respectfully traverses the 35 U.S.C. § 102(a) and (b) rejections of Applicants' claims 13, 20, 30 and 34 over the cited references Benito and Brennan. Claims 30-38 were amended pursuant to the Examiner's suggestion. As such, claims 30 and 34 are patentable over the cited art.

To anticipate a claim a reference must contain all of the elements of the claim. *Hybritech, Inc.* v. *Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986); *In re Marshall*, 578 F.2d 301 (C.C.P.A. 1978).

Benito et al. teach incorporation of a linear viral epitope (main antigenic region of foot-and-mouth disease virus serotype C_1) into a sequence of β-galactosidase. Brennan et al. clearly teach incorporation of a linear viral epitope (epitope from HIV-1 protein V3 loop) into a sequence of bacterial alkaline phosphatase. Benito et al. and Brennan et al. do not teach or suggest incorporation of mimetopes into a starting sequence of enzyme. Also Benito et al. and Brennan et al. do not anticipate the subject matter of currently pending claims 30 and 34. The currently amended claims 30 and 34 teach chimeric β-lactamase having regulatable activity. Making of a chimeric β-lactamase is not taught or suggested in the cited references.

Thus, Benito et al. and Brennan et al. do not teach or suggest all of the limitations of the currently pending claims 13, 20, 30 and 34. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference" *Verdegaal Bros. V. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). (See, MPEP 2131).

Therefore, Benito et al. and Brennan et al. do not anticipate the subject matter of currently pending claims 13, 20, 30, and 34. Thus, withdrawal of this rejection is respectfully requested.

D. Conclusion

In view of the comments herein, the present application is believed to be in condition for allowance or in better condition for an appeal. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

If there are any further points requiring attention prior to allowance or if these remarks do not place the rejected claims in condition for allowance, then Applicants respectfully request the courtesy of a telephonic interview.

No additional fee is required. If there any such fees, please charge them to our firm Deposit Account No. 50-0540.

Respectfully submitted,

July 8, 2003

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EXHIBIT A

MARKED UP VERSION OF AMENDED CLAIMS 30, 34, 37 AND 38

(Additions underlined, deletions bracketed)

30. (Amended) A method for determining the presence or amount of an analyte in a test sample, comprising:

forming a mixture of (1) a chimeric enzyme comprising <u>β-lactamase</u> [an enzyme] and a binding site moiety, said binding site moiety including at least one amino acid, said chimeric enzyme having a sequence of said binding site moiety inserted in said enzyme or replacing at least one amino acid of said enzyme with the proviso that the activity of the chimeric enzyme is modulated upon binding of a binding molecule to the binding site moiety, (2) a test sample containing said analyte of interest, (3) a binding molecule which binds to a binding site moiety of the chimeric enzyme and modulates the activity of the enzyme, and (4) a substrate upon which the chimeric enzyme catalytically acts; and

detecting the amount of catalysis of the substrate and thereby determining the presence or absence of said analyte of interest.

34. (Amended) A method for determining the presence or amount of an analyte in a test sample, comprising:

forming a mixture of (1) a chimeric enzyme comprising <u>β-lactamase</u> [an enzyme] and a binding site moiety, said binding site moiety including at least one amino acid, wherein said chimeric enzyme having a sequence of said binding site moiety inserted in said enzyme or replacing at least one amino acid of enzyme with the proviso that the activity of the chimeric

enzyme is modulated upon binding of a binding molecule to the binding site moiety, (2) test sample containing said analyte of interest, and (3) a substrate upon which the chimeric enzyme catalytically acts; and

detecting the amount of catalysis of the substrate and thereby determining the presence or absence of said analyte of interest.

37. (Amended) The method of claim 30, wherein the enzymatic activity of the chimeric enzyme in the unbound state is equivalent to that of the β-lactamase [starting enzyme].

38. (Amended) The method of claim 34, wherein the enzymatic activity of the chimeric enzyme in the unbound state is equivalent to that of the β-lactamase [starting enzyme].